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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,498	07/07/2003	Alan P. Kozikowski	GUX-012.01	8108

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EXAMINER	
DESAI, RITA J	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
02/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/614,498	KOZIKOWSKI ET AL.	
	Examiner	Art Unit	
	Rita J. Desai	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,32,41,50,60-62,64,73-81,90 and 91* is/are pending in the application.

4a) Of the above claim(s) *41,50,60-62,64,73-81,90 and 91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/9/07,6/18/07*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

Claims 1-8, 32, 41, 50, 60-62, 64, 73-81, 90 and 91 are pending.

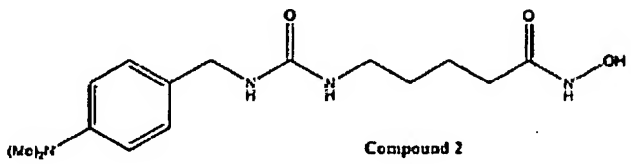
Claims 9-31, 33-40, 42-49, 52-59, 65-72 and 82-89 are cancelled.

The claims under consideration currently are 1-8 and 32 as rejoined by the examiner ion the office action mailed 5/8/2006.

Applicants have elected group II of the restriction claims 1-8,32 in part drawn to formula I wherein R1 is a aryl. The examiner has rejoined group I and III in part wherein R1 is a cycloalkyl.

Thus now the group includes R1 to be an aryl, cycloalkyl and a hetero cyclo.

The species that was elected was



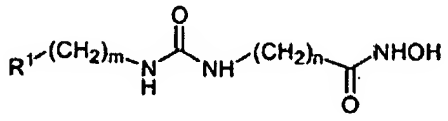
Compound 2

Claim Rejections - 35 USC § 103

The rejection of the claims 1-8 and 32 over Richon et al 1998 , and Watkins WO 0226696 , 2002 still stands.

Applicants argue that the examiner has not made a prima facie case. This is incorrect.

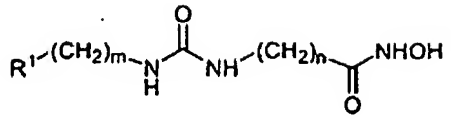
Applicants compounds are given by the following on page 14. m is 1 or 2.



Compound No.	R^1	m	n
1	Phenyl	2	3
2	4-$N(CH_3)_2$-Phenyl	1	3
3	4-$N(CH_3)_2$-Phenyl	1	4
4	4-$N(CH_3)_2$-Phenyl	1	5
5	4-$N(CH_3)_2$-Phenyl	1	6
6	4-$N(CH_3)_2$-Phenyl	1	7

and pharmaceutically acceptable salts thereof.

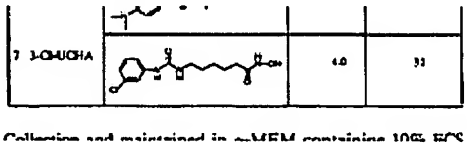
On page 16 applicants disclose



Compound No.	R^1	m	n
7	4-$N(CH_3)_2$-Phenyl	0	6
8	Adamantyl	0	5

wherein m is a zero.

Richon et al teaches the compound

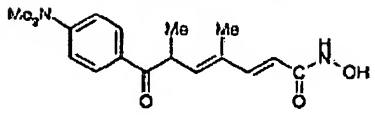


This compound differs in that m is 0 .

The use of these compounds is the same .

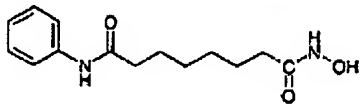
The Watkin WO 0226696 reference teaches

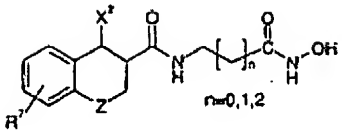
Trichostatin A (TSA)

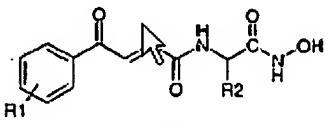


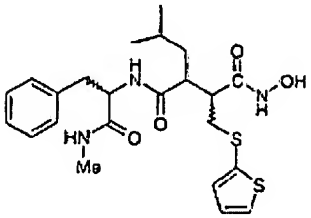
15

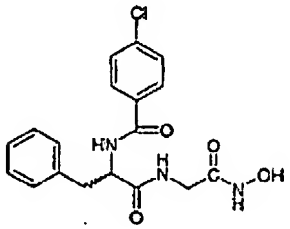
Suberoylanilide Hydroxamic Acid (SAHA)



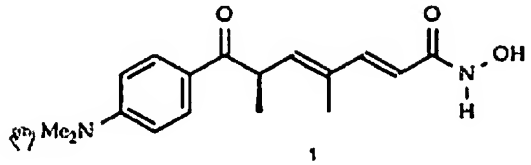








Watkin referes to the Richon and Jung et al 1997, 1999.



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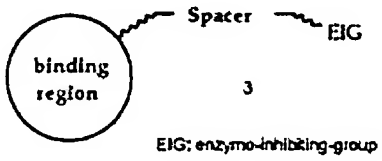
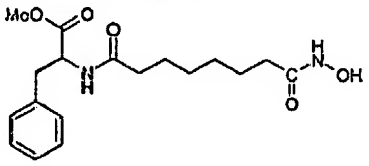


M. Jung et al .

Jung et al., 1997, 1999, describe several aromatic hydroxamic acid compounds which apparently inhibit HDAC. Some of the compounds have a phenylamido group (PhCONH-). One compound, a peptide analog, is shown below (see, e.g., compound 6 in Jung et al., 1997; compound 4 in Jung et al., 1999).



(applicants specifications page 10.)

Jung et al teaches that there is a binding region and an enzyme inhibiting group is seperarted by a spacer.

A variety of spacers are disclosed.

Thus the prior art teaches that the link of the phenyl ring can be attached to the N of the urea or to a carbon atom and it would still retain its properties.

This would motivate a person of skill in the art to modify the compounds to m =1 -4 (lower alkyl) and still expect the maintain the properties. In other words knowledge of the prior art compounds would have motivated one of skill in the art to modify the chain from m=0 to m =1 to 4, CH2 linkage to obtain the compound of the instant invention.

Thus the 103 rejection has been maintained

The rejection of claims 1-8 and 32 under 35 USC 112 first paragraph also still stands.

The rejection is on how to make and how to use the claimed invention.

See Methot et al , 2008 , page 2, which teaches that all structures do not have the same activity.

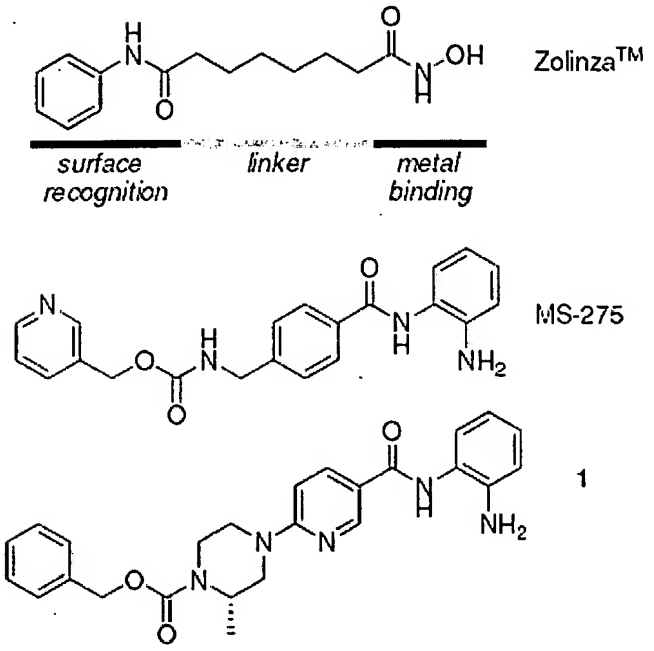


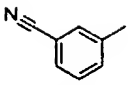
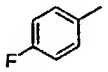
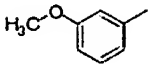
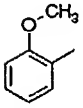
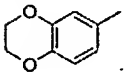
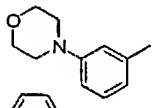
Figure 1. HDAC inhibitors Zolinza™, MS-275, and piperazyl benzamide 1.

inhibitors containing a hydroxamic acid moiety in the zinc-binding motif, Zolinza™ (SAHA, vorinostat) is a broad-spectrum HDAC inhibitor. Another class of HDAC inhibitors contains an α-aminobenzamide zinc-binding motif as exemplified by MS-275[6] (SNDX-275) and nicotinyl piperazine 1.[7] As is typically observed for benzamide-derived inhibitors, compound 1 inhibits HDACs 1–3 but does not significantly inhibit the other HDAC isoforms screened. Though the histone deacetylase family is well documented in the development of cancer, the role of the individual HDACs remains unclear. HDACs 1 and 2 share a high degree of homology and are found in the same multicomponent nuclear complexes containing transcriptional co-repressors such as mSin3 and NuRD.[8] They both have been shown to be overexpressed in human cancers and knockdown leads to increased apoptosis.[9]

Also see Siliphaivanh 2007, page 4621

Encouraged by the activity of benzamide 5a, our attention was directed toward the synthesis of analogues with diverse substitution around the phenyl ring in the surface recognition domain. Representative analogues (Table 1) demonstrate that a wide array of functionality can be tolerated in the malonyl–phenyl rings including nitrile, methoxy, and morpholine moieties. A reduction in cellular potency can be seen in biaryl 5i, possibly due to its low hydrophilicity. The clog P^{23} of 5i is greater than that of the phenyl amide 5a by two log units. Notably, ortho-substitution of the malonyl–phenyl rings was tolerated in contrast to ortho-substitution of the phenyl ring within vorinostat, which leads to a marked decrease in activity.

Moreover, both amide NH moieties were essential for significant enzymatic and cellular potency (Table 2). Incorporation of a single methyl group on the malonyl sidechains to give 5j resulted in a 5-fold loss of potency. Similarly, the dimethyl derivative 5k was 100-fold less potent indicating that hydrogen bonding, either inter- or intra-molecular, may play an important role in the recognition of the HDAC active site. Similarly, it was shown that malonyl di-ester analogues possessed significant reduction in HDAC enzymatic activity as well (data not shown).

5b		34	500[a]
5c		63	222[a]
5d		56	607
5e		35	383
5f		47	394
5g		21	220
5h		45	542
5i		103	1200

The quinoline substituted compound had a lower potency.

Thus the substitution and the with the activity is very unpredictable.

The state of the art is unpredictable. The only compounds made by the applicants are the ones wherein R1 is a phenyl.

Even though the claim recites 3-10 heterocyclic and cycloalkyls which can be still further substituted.

Thus when the art is so unpredictable the applicants should provide more guidance with the examples commensurate to the scope of the claims.

So in view of the above the arguments presented by the applicants are not convincing.

The examiner has provided sufficient evidence , regarding the unpredictability of this pharmaceutical art.

Hence the rejection still stands.

The previous rejections a re repeated here for convenience.

The arguments do not overcome the rejection of claim s1-8 and 32 under 35 USC 112 rejection under first paragraph .

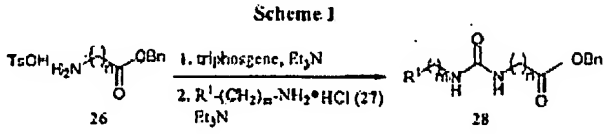
Applicants claims with the option wherein R1 can be any 3 to 10 membered hetrocyclic group itself covers numerous groups from pyridyl, piperazine , thienyl, furan, quinoline, and so on and so on. Then the aryl groups could be many other options. One skilled in the art would understand that a pyridyl has different electro negativity and properties than a thienyl or a piperazine. The example given by the examiner of theophylline verses caffeine. Is still valid. Caffeine even though structurally so similar (H Vs a methyl group) is not marketed as a broncodialator. Quinolines are generally used as a bactericide. A hetero cylic group or a cycloalkyl group would definitely be different than a phenyl or an admantyl and as such should have more showing that it is a "pharmaceutical".

The rejection of claims 1-8 and 32 under 35 USC 112 first paragraph still stands.

Applicants argue that

The synthetic Scheme 1 (page 31 of the instant Application; reproduced in pertinent part below), wherein the Applicants provide a straightforward synthetic approach to the desired urea compounds of the invention via reaction (in step 2) of a primary amine with an electrophilic isocyanate intermediate (formed in step 1).

Scheme 1



This is not convincing because the rejection is based on 2 parts, make and use. The use of these compounds in pharmaceutical uses is highly unpredictable and as such the applicants should have enable them.

Applicants argue that on pages 70-85 in table 3 and 4 applicants have provided a lot of data to demonstrate inhibition.

This may be so , however all the compounds shown have either a phenyl or an admantyl, and this does not cover the scope of applicants generic claims of the aryl cycloalkyl or 3to 10 membered hetero cycle.

Thus the rejection still stands.

The rejection of claims 1-8 and 32 still stands.

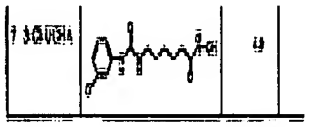
Solely on the Richon et al reference the compounds are homologs with a difference of one -CH2- group.

Applicants arguement that this is an oversimplification is not correct.

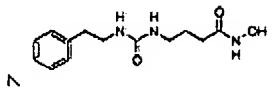
If the compound 7 of the Richon reference is compare to the compounds, it reads on the compounds when , R1 is a phenyl m is o, and n is 5.

Thus the difference is only of m being more 1.

Richons compounds is

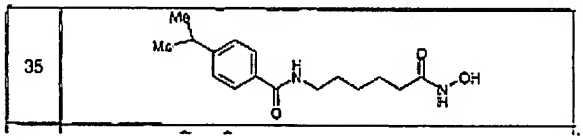


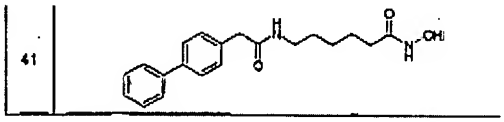
Applicants compound is

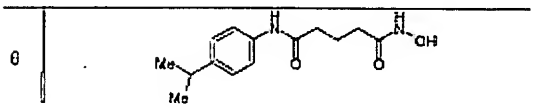


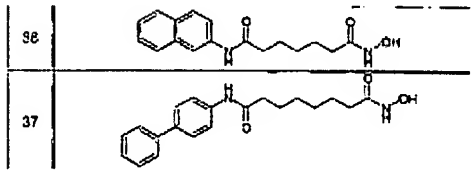
Similar compounds in WO 0226696 Watkins et al are also taught.

The WO patent teaches the compounds









Clearly the equivalency of the linkage to the N or the Ch2 for the R1 is equivalent. The compounds have a similar activity i.e. are HDAC inhibitors. And with the teaching of the equivalence of the linkages, there is a motivation to modify them to obtain the compounds of the invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> *The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

Claims 1-8 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for R1 to be a phenyl and adamantly , does not reasonably provide enablement for any other cylcoalkyl or any 3-10 membered heterocylic group. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims: *The instant claims encompass many compounds from an aromatic carbocyclic moiety to an aromatic carbocyclic moiety having many large electron withdrawing and bulky groups substituted on it to a moiety having many heterocyclic rings. These compounds cover a very wide range of compounds.*

2) The nature of the invention: *The invention is a hydroxyamido compound that is useful to treating cancer.*

3) The state of the prior art: *The state of the prior art is that the drugs and the enzymes react in a lock and key mechanism and the structure of the compound has to be specific. Even a difference of a methyl group verses a hydrogen changes the properties altogether. A good example is a theophylline verses caffeine . They differ by just a methyl group but one of them has a pharmaceutical use as a bronchodilator. There is no absolute predictability and no established correlation between the different substitutions on a core that they would all behave in the exact same way. Applicants R1 is drawn to hetero ring and cycloalkyl and also aryls. Hetero ring due to the presence of other atoms such a N, S and O have different electronegativity and hence bonding and properties. Thus they would not behave in the same way as a an aryl. Also there is very little known in the treatment of cancer and the state of the prior art is that it involves screening in vitro and invivo to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability and no established correlation between in vitro activity and the treatment of any and all cancers, as the in vitro data is not a reliable predictor of success even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.*

4) The level of one of ordinary skill: *The ordinary artisan is highly skilled.*

5) The level of predictability in the art: *It is noted that the pharmaceutical art is unpredictable , requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. The level of unpredictability is in the art is very high. The compounds which differ by a methyl group also show different properties, for e.g. theophylline and caffeine. One of them is a bronchodialator and they differ only by a methyl group.*

6) The amount of direction provided by the inventor: *The inventor provides very little direction in the instant specification. There are no examples with the R being hetero cyclic groups and also there is no data provided to show that these compounds do indeed treat cancer or even have any histone deacetylase activity.*

7) The existence of working examples: *The instant specification does not have any working examples nor any invitro or invivo data that they do have any activity.*

8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: *Since there are no working examples, the amount of experimentation is very high and burdensome.*

Taking the above eight factors into consideration, it is not seen where the instant specification enables the ordinary artisan to make and/or use the instantly claimed invention.

Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001.

"A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention , not for vague intimations of general ideas that may or may not be workable."

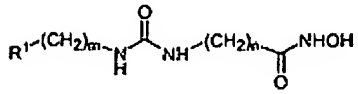
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

Claims 1-8 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable overVictoria Richon et al 1998 and also WO0226696 Watkins et al 2002.

Applicants claims are drawn to



(I) *wherein R1 is an aryl, or a cycloalkyl or a heterocylcoalkyl,*

Determination of the scope and content of the prior art (MPEP §2141.01)

The reference Richon et al teaches various compounds, see table 1 page 3004 . particularly compound 7 .

Also see the teaching on page 3005 that UCHA is the most potent HPC.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The compound 7 of the prior art differs by just one CH2 linkage since applicants m is 1 to 10.

The reference teaches the structural similarity is the terminal hydromic group.

See the results section on page 3004.

WO0226696 Watkins et al 2002 on page 57 aryl and heteroaryl groups not directly linked. See compound 46, 48, 49 on page 57. These compounds are also HDAC inhibitors

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

Thus with the prior art teaching that these similar compounds have an activity to inhibit histone deacetylases and also with the teaching of the various groups as given in the table 1 of the Richon reference and the compounds as given on page 57 of the WO'696 document , one would be motivated and would find it prima facie obvious to make a compound which was not directly linked to the NH-C(O)-NH to obtain the compounds of the invention.

Conclusion

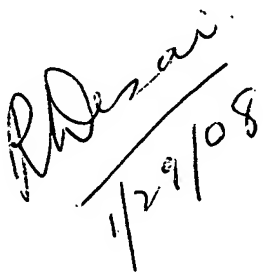
Claims 1-8 and 32 stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita J. Desai whose telephone number is 571-272-0684. The examiner can normally be reached on Monday - Friday, flex time..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rita J. Desai
Primary Examiner
Art Unit 1625



R.D.
January 29, 2008